WEST Search History

DATE: Tuesday, October 15, 2002

Set Name side by side	Query	Hit Count	Set Name result set
	DB=USPT; PLUR=YES; OP=OR		
L13	(((interferon-gamma or (interferon adj gamma)).ab.) and ((interferon-gamma or (interferon adj gamma))and ((interferon with (alpha or beta)) or interleukin or TNF or caboquone or cyclophosphamide or aclarubicin or thiotepa or busulfan or ancitabine or cytarebine or $uracil or methotrexate or actinomycin or chromycin or daunorubicin or doxorubicin or bleomycin oor mitomycin or vincristine or vinblastine or l-asparaginase or (radio adj gold adj colloidal) or Krestin or picibanil or lentinan or (maruyama adj vaccine))))	70	L13
L12	((interferon-gamma or (interferon adj gamma)) .ab.)	77	L12
L11	((interferon-gamma or (interferon adj gamma)) and ((interferon with (alpha or beta)) or interleukin or TNF or caboquone or cyclophosphamide or aclarubicin or thiotepa or busulfan or ancitabine or cytarebine or $uracil or methotrexate or actinomycin or chromycin or daunorubicin or doxorubicin or bleomycin oor mitomycin or vincristine or vinblastine or l-asparaginase or (radio adj gold adj colloidal) or Krestin or picibanil or lentinan or (maruyama adj vaccine)))	2584	L11
L10	(interferon-gamma or (interferon adj gamma))	2836	L10
L9	5134076.pn.	1	L9
L8	L7 and @ad<19951115	2	L8
L7	(interferon adj gamma adj inducing adj factor) or (IGIF and interferon)	73	L7
L6	L4 and l3	70	L6
L5	L4 and l2	70	L5
L4	l1.ab.	77	L4
L3	L2 and @ad<20001121	2538	L3
L2	L1 and ((interferon with (alpha or beta)) or interleukin or TNF or caboquone or cyclophosphamide or aclarubicin or thiotepa or busulfan or ancitabine or cytarebine or $uracil or methotrexate or actinomycin or chromycin or daunorubicin or doxorubicin or bleomycin oor mitomycin or vincristine or vinblastine or l-asparaginase or (radio adj gold adj colloidal) or Krestin or picibanil or lentinan or (maruyama adj vaccine))	2584	L2
L1	interferon-gamma or (interferon adj gamma)	2836	L1

END OF SEARCH HISTORY

Generate Collection

L6: Entry 8 of 70 File: USPT Dec 11, 2001

DOCUMENT-IDENTIFIER: US 6329365 B1
TITLE: Inhibitors of interleukin-1.beta. converting enzyme

DATE FILED (1):
19990604

Abstract Text (1):
The present invention relates to novel classes of compounds which are inhibitors of interleukin-1.beta. converting enzyme ("ICE"). This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against interleukin-1-("IL-1"), apoptosis -, interferon-.gamma. inducing factor-(IGIF), interferon-.gamma. -("IFN-.gamma.") mediated diseases, excess dietary alcohol intake diseases, or viral diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. This invention also relates to methods for inhibiting ICE activity and decreasing IGIF production and IFN-.gamma. production and methods for treating interleukin-1, apoptosis- and interferon-.gamma. -mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing the compounds of this invention.

Brief Summary Text (2):
The present invention relates to novel classes of compounds which are inhibitors of interleukin-1.beta. converting enzyme ("ICE"). This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against interleukin-1-("IL-1"), apoptosis -, interferon-.gamma. inducing factor-(IGIF), interferon-.gamma. -("IFN-.gamma.") mediated diseases, excess dietary alcohol intake diseases, or viral diseases, including inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, and degenerative diseases. This invention also relates to methods for inhibiting ICE activity and decreasing IGIF production and IFN-.gamma. production and methods for treating interleukin-1, apoptosis- and interferon-.gamma. -mediated diseases using the compounds and compositions of this invention. This invention also relates to methods of preparing the compounds of this invention.

Brief Summary Text (4):
Interleukin 1 ("IL-1") is a major pro-inflammatory and immunoregulatory protein that stimulates fibroblast differentiation and proliferation, the production of prostaglandins, collagenase and phospholipase by synovial cells and chondrocytes, basophil and eosinophil degranulation and neutrophil activation. Oppenheim, J. H. et al., Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. For example, in rheumatoid arthritis, IL-1 is both a mediator of inflammatory symptoms and of the destruction of the cartilage proteoglycan in afflicted joints. Wood, D. D. et al., Arthritis Rheum. 26, p. 975, (1983); Pettipher, E. J. et al., Proc. Natl. Acad. Sci. U.S.A. 71, p. 295 (1986); Arend, W. P. and Dayer, J. M., Arthritis Rheum. 38, p. 151 (1995). IL-1 is also a highly potent bone resorption agent. Jandiski, J. J., J. Oral Path 17, p. 145 (1988); Dewhirst, F. E. et al., J. Immunol. 8, p. 2562 1985). It is alternately referred to as "osteoclast activating factor" in destructive bone diseases such as osteoarthritis and multiple myeloma. Bataille, R. et al., Int. J. Clin. Lab. Res. 21(4), p. 283 (1992). In certain proliferative disorders, such as acute myelogenous leukemia and multiple myeloma, IL-1 can promote tumor cell growth and adhesion. Bani, M. R., J. Natl. Cancer Inst. 83, p. 123 (1991);

Vidal-Vanaclocha, F., Cancer Res. 54, p. 2667 (1994). In these disorders, IL-1 also stimulates production of other cytokines such as IL-6, which can modulate tumor development (Tartour et al., Cancer Res. 54, p. 6243 (1994). IL-1 is predominantly produced by peripheral blood monocytes as part of the inflammatory response and exists in two distinct agonist forms, IL-1.alpha. and IL-1.beta.. Mosely, B. S. et al., Proc. Nat. Acad. Sci., 84, pp.4572-4576 (1987); Lonnemann, G. et al., Eur.J. Immunol., 19, pp.1531-1536 (1989).

Brief Summary Text (5):
IL-1.beta. is synthesized as a biologically inactive precursor, pIL-1.beta.. pIL-1.beta. lacks a conventional leader sequence and is not processed by a signal peptidase. March, C. J., Nature, 315, pp.641-647 (1985). Instead, pIL-1.beta. is cleaved by interleukin-1.beta. converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P. R. et al., J. Biol. Chem., 265, pp.14526-14528 (1992); Howard, A. D. et al., J. Immunol., 147, pp.2964-2969 (1991). ICE is a cysteine protease localized primarily in monocytes. It converts precursor IL-1.beta. to the mature form. Black, R. A. et al., FEBS Lett., 247, pp.386-390 (1989); Kostura, M. J. et al., Proc. Natl. Acad. Sci. U.S.A., 86, pp.5227-5231 (1989). Processing by ICE is also necessary for the transport of mature IL-1.beta. through the cell membrane.

Brief Summary Text (11):
Interferon-gamma inducing factor (IGIF) is an approximately 18-kDa polypeptide that stimulates T-cell production of interferon-gamma (IFN-.gamma.). IGIF is produced by activated Kupffer cells and macrophages in vivo and is exported out of such cells upon endotoxin stimulation. Thus, a compound that decreases IGIF production would be useful as an inhibitor of such T-cell stimulation which in turn would reduce the levels of IFN-.gamma. production by those cells.

Brief Summary Text (31):
The term "interferon gamma inducing factor" or "IGIF" refers to a factor which is capable of stimulating the endogenous production of IFN-.gamma..

Brief Summary Text (182):
The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha-interferon antibody, IL-2, GM-CSF, methionine enkephalin, interferon-alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and EPO), with prostaglandins, or with antiviral agents (e.g., 3TC, polysulfated polysaccharides, ganiclovir, ribavirin, acyclovir, alpha interferon, trimethotrexate and fancyclovir) or prodrugs of these or related compounds to prevent or combat IL-1-mediated disease symptoms such as inflammation.

Detailed Description Text (51):
Processing of pre-IL-1.beta. by ICE can be measured in cell culture using a variety of cell sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of interleukins and cytokines in response to many classes of physiological stimulators. Adherent mononuclear cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Detailed Description Text (113):
R & D Systems (614 McKinley Place N.E. Minneapolis, Minn. 55413) Quantikine kits may be used for measurement of IL-1.beta. and TNF-.alpha.. The assays are performed according to the manufacturer's directions. IL-1.beta. levels of .about.1-5 ng/ml in positive controls among a range of individuals may be observed. A 1:200 dilution of plasma for all samples is usually sufficient for experiments for ELISA results to fall on the linear range of the ELISA standard curves. It may be necessary to optimize standard dilutions if you observe differences in the whole blood assay. Nerad, J. L. et al., J. Leukocyte Biol., 52, pp. 687-692 (1992).